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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BAUSCH, SARAE L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,947	DAHLBACK, BJORN	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46,53-55,64 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46, 53-55, 64-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Currently, claims 46, 53-55, and 64-65 are pending in the instant application. Claims 64-65 are newly added and claims 1-45, 47-52, and 56-63 are canceled. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. They represent the complete being presently applied to the instantly examined claims. Response to arguments follow. This action is FINAL.

2. The examiner in this application has changed. All previous prosecution history including previously filed IDS have been considered. Please address future correspondence to Examiner Sarae Bausch, Art Unit 1634.

Withdrawn Rejections

3. The rejections of claims 54-63, under 35 U.S.C. 112, second paragraph, made in section 6, page 2-3, of the previous office action, is withdrawn in view of the amendment to the claims.

New Grounds of Rejections

Claim Rejections - 35 USC § 112, 1st ¶

4. Claims 46, 53-55, 64-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention. It is noted that this rejection was previously presented in section 11 of the 06/08/2004 and has been rewritten to accommodate the amendment to claims 46, 53-55 and newly added claims 64 and 65.

Nature of the Invention

The invention is drawn to methods for predicting an increased risk of developing thrombosis and/or APC resistance caused by a gene mutation via screening of samples for the occurrence of Factor V gene mutations that give rise to the expression of a mutated Factor V/Va molecule. Thus, the nature of the invention requires the knowledge of a mutation in the Factor V gene which is associated with an increased risk of developing thrombosis and/or APC resistance.

Breadth of the Claims

Claim 46 is drawn to a method for determining an increased risk of developing thrombosis and contains a single method step of comparing the individual's Factor V gene sequence to a normal Factor V gene sequence. The implication of the claim is that the determination of risk is based on an abnormality of the patient's gene sequence, though the claim does not give the structure of the abnormality. Claim 53 depends from claim 46 and requires the genes are compared via sequencing. Claim 65 depends from claim 53 and requires that the sequencing assay uses reagents specific for Factor V gene. Claim 65 depends from claim 64 and requires detecting an abnormal nucleotide sequence in Factor V gene.

Claim 54 is drawn to a method for identifying an occurrence of a Factor V gene mutation associated with APC-resistance comprising determining an occurrence of the mutation in the Factor V gene locus. Claims 55-61 depend from claim 54.

Thus, the claims encompass screening methods which detect any mutation within the Factor V gene, with some claims requiring that the mutation give rise to the expression of a mutated Factor V/Va molecule.

Teachings of the Specification, Working examples

The specification teaches at ¶ 0081 that a "neutral polymorphism" in the Factor V gene has linkage with inherited APC resistance. The specification does not give the structure of the polymorphism, i.e. wherein within the gene the polymorphism is located or what base change occurs, nor does the specification disclose any polymorphism or mutation within the Factor V gene that result in the expression of a mutated factor V/Va molecule.

There are no working examples in the specification which exemplify an embodiment of the claimed methods.

State of the Prior Art

The prior art does not provide any genetic variations within the Factor V gene that are associated with thrombosis or APC resistance.

Level of Unpredictability

There is a large body of knowledge in the art related to polymorphisms in general, and their association with diseases or disease states. Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). In some cases where multiple polymorphisms are identified in a gene, some

of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The instant application does not teach any mutations or polymorphisms within the human Factor V gene. There is a disclosure that a single "neutral polymorphism" is known to exist, but there is not disclosure of the polymorphisms itself such that it could be used in an assay to predict the presence of the phenotype. It is highly unpredictable which nucleotides within the human Factor V gene are the polymorphic or mutated nucleotides that are associated with disease.

Quantity of Experimentation

The quantity of experimentation necessary to practice the claimed invention is quite high, and would involve the screening and analysis of the Factor V gene from hundreds of patients to identify any putative polymorphisms and mutations within the gene and to establish a relationship between these and the recited phenotypes.

Conclusion

Considering all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks

Applicant's response summarizes in re Wands case law on pages 4-5.

Applicant asserts on page 5-6 of the response that contrary to the Examiner's notion that the specification does not provide conclusive evidence of Factor V gene's involvement in thrombosis associated with APC-resistance, the specification does provide clinical and biochemical evidence leading to the conclusion that Factor V has a novel anticoagulant activity and that deficiency of such activity causes thrombosis associated with APC-resistance. Applicants point to several places in the specification that provide this evidence, for example page 3 lines 21 to page 4 line 15 and page 6 line 4 to page 7 line 12. This response has been thoroughly reviewed but not found persuasive. First, the examiner's assertion was that the specification does not provide conclusive evidence that a mutation in Factor V gene is a cause of an increased risk of developing thrombosis in an individual or associated with APC-resistance (see page 3, last paragraph of the previous office action). The specification on page 3-4 suggests that the APC-resistance is correlated to thrombosis, however the APC resistance disclosed in the specification does not suggestion or show a correlation between any mutation in the Factor V gene and thrombosis. Additionally, the APC resistance which is disclosed on pages 2-3 and 6-7 of the specification is not required for the claimed invention. The claims require a method of determining APC resistance or detecting an individuals risk of thrombosis by determining the presence of a Factor V gene mutation, which the specification does not describe. The specification does not teach a correlation between "any" mutation in "any" Factor V gene and an association with thrombosis or APC resistance. Furthermore, the practice of the claimed

methods requires the identification of mutations within and linked to the Factor V gene which are not described and the specification does not provide any description beyond suggesting that they might exist. While applicant is not claiming nucleic acids comprising these mutations, known mutations within the nucleic acid that is correlative to an increased risk of thrombosis are essential for the practice of the claimed method.

Applicant further argues on page 7, 1st full paragraph of the response, that it was known in the art before the relevant priority date of the present application that APC inactivates activated bovine Factor V by cleavage at least at position Arg505 which corresponds to Arg506 in human Factor V. The response asserts that therefore based on the teachings in the specification of the present application and the knowledge in the art one of skill would readily have concluded that a mutation in the Factor V gene is the most likely cause for thrombosis associated with APC-resistance. This response has been thoroughly reviewed but not found persuasive. The claims are not drawn to APC inactivation, the claims are drawn to a method of determining an increased risk of thrombosis based on the presence of a mutation in factor V gene. Furthermore, one of skill in the art would not be able to readily conclude that a mutation in Factor V gene is the most likely cause for thrombosis. As described on page 6-7 of the office action mailed 06/08/2004, even if a mutation is present in a gene this does not necessarily correlate to an association with a disease. For example, Blumenfeld et al. teach that multiple mutations in a gene were identified however not all of these mutations were associated with patients having the disease. Therefore, even if a mutation was present in Factor V and the skilled artisan assayed for any mutation, the mutation present may not be associated with any disease. The fact that a mutation in Arg505 in bovine Factor V is inactivated by APC does not provide

evidence that a correlation of the same mutation in human Factor V gene would have the same affect by APC nor does the inactivation of APC correlate with an increased risk of developing thrombosis, as required by the claims. The fact that the Factor V gene may be associated with APC resistance is not sufficient written description to support the claimed methods which require the identification and/or assay of mutations within the gene as no mutations are taught in the specification nor are the mutations taught in the prior art. One teaching of APC inactivation of bovine factor V by the presence of a mutation at position Arg505 does not represent the claimed genus nor does the presence of a mutation show a correlation between "any" mutation in Factor V gene and an increased risk of thrombosis in "any" individual. Not only is the specification not enabled for a method of determining an individual's risk of thrombosis but the specification does not describe a single example within the claimed genus.

Applicant further asserts on page 8, 1st paragraph of the response, that the specification of the present invention provides reasonable guidance or directions on how to carry out the methods to detect a mutation in the Factor V gene as claimed in claims 46 and 54. The response asserts that on page 20, lines 8-23 the specification teaches how to carry out nucleic acid assays in order to detect an individual at risk of developing thrombosis. This response has been thoroughly reviewed but not found persuasive. The methods steps of sequencing and hybridization assay a nucleic acid is enabled, however what is not enable is a method of identifying a person at risk for thrombosis by detecting a mutation in Factor V gene nor is the method of determining the presence of a mutation of Factor V gene mutation association with APC-resistance. The specification does not enable one of skill in the art to determine which mutations in Factor V gene would correlate to identification of a person at risk for thrombosis or correlate with the

association of APC-resistance. Furthermore for one of skill in the art to predictably correlate any mutation in Factor V gene with the risk of developing thrombosis in an individual, as well as APC-resistance would require undue experimentation. The skilled artisan would have to perform an extremely large study and include different populations to determine if in fact there is an association with "any" mutation in Factor V gene and thrombosis and APC-resistance. The results of such a study are clearly unpredictably, as discussed on page 6-7 of the office action mailed 06/08/2004 coupled with the lack of teaching in the specification of "any" mutation of Factor V gene. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine mutations with the Factor V gene both in patients with thrombosis, APC-resistance and healthy subjects, which would require performing an extremely large amount of trial and error analysis in a large study to determine the correlation of every mutation and its predictability to thrombosis and APC-resistance. Given that the specification does not teach any mutations in the Factor V gene and lack of guidance in the prior art at the time of the priority date, the analysis of determining a mutation in Factor V gene that is correlative to APC-resistance, such analysis is replete with unpredictable experimentation and is undue experimentation.

The response asserts on page 8, 2nd full paragraph that the present application provides conclusive evidence that Factor V gene's involvement of thrombosis associated with APC-resistance and provides reasonable guidance or directions on how to practice the invention. This response has been thoroughly reviewed but not found persuasive. The specification does not enable one of skill in the art to determine an individual's risk of developing thrombosis nor determining APC-resistance by determining a mutation in Factor V gene because the

specification does not teach any Factor V gene mutations associated with either a risk of developing thrombosis or APC-resistance.

Applicants assert on page 9, 2nd full paragraph, that there was a high level of knowledge about Factor V gene and protein in the art at the time when the application was filed allowing one of ordinary skill in the art to determine possible mutations that could cause APC-resistance. This response has been thoroughly reviewed but not found persuasive. While knowledge of Factor V gene and protein was known at the time the application was filed, mutations within the Factor V gene were not known nor was an association with thrombosis or APC-resistance. Neither the prior art nor the specification, at the time the application was filed, teach mutations within the Factor V gene and a correlation between APC-resistance or thrombosis.

Applicants asserts on page 9, last paragraph, continued to page 10, 1st full paragraph, that it was well within the routine skill of an ordinary artisan to determine what amino acid substitution would be silent or cause only conservative substitution and what amino acid substitutions would alter a protein's function. Applicants asserts that a skilled artisan would have readily been able to isolate and amplify nucleic acids from lymphocytes of an individual who showed APC-resistance or was at risk of thrombosis associated with APC-resistance. This response has been thoroughly reviewed but not found persuasive because although amino acid substitution, isolation, and amplification of nucleic acids are routine assays the method of predictably correlating and determining a risk of thrombosis or APC-resistance by any mutation in Factor V gene is not a routine assay. As stated above, for one of skill in the art to predictably correlate any mutation in Factor V gene with the risk of developing thrombosis in an individual, as well as APC-resistance would require undue experimentation. The skilled artisan would have

to perform an extremely large study and include different populations to determine if in fact there is an association with "any" mutation in Factor V gene and thrombosis and APC-resistance. The results of such a study are clearly unpredictably, as discussed on page 6-7 of the office action mailed 06/08/2004 coupled with the lack of teaching in the specification of "any" mutation of Factor V gene. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine mutations with the Factor V gene both in patients with thrombosis, APC-resistance and healthy subjects, which would require performing an extremely large amount of trial and error analysis in a large study to determine the correlation of every mutation and its predictability to thrombosis and APC-resistance. Given that the specification does not teach a single mutation in the Factor V gene and coupled with the lack of guidance in the prior art at the time of the priority date with determining an association of a mutation in Factor V gene and thrombosis or APC-resistance, the analysis of determining a mutation in Factor V gene that is correlative to APC-resistance and thrombosis is replete with unpredictable experimentation and is undue experimentation.

The response asserts on page 10, last paragraph continued to page 11, 1st full paragraph that based on the teaching of Voorberg et al., who determined post-filing a mutation at position Arg506 of factor V gene that is correlative to thrombosis that these experiments were routine experimentations and none were undue. This response has been thoroughly reviewed but not found persuasive. Voorberg et al. is post filing art, at the time the invention was filed the experimentation to predictably correlative "any" mutation in Factor V gene with thrombosis or APC-resistance is undue. The specification does not describe a single mutation in Factor V gene and coupled with the lack of guidance in the art and post filing art, as stated above, by

Blumenfeld et al. that teaches multiple mutations in a gene are not all correlative with a disease, the experimentation is unpredictable and undue.

The response asserts on page 11, last paragraph, that the present specification is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation because the specification provides sufficient support for a novel anticoagulant activity of Factor V gene and there was a high level of knowledge about the Factor V gene and protein at the time the application was filed and all the methods and tools were well known in the art. This response has been thoroughly reviewed but not found persuasive. Although the assays to sequence nucleic acids were known in the art, the ability to predictably correlation "any" mutation in Factor V gene with any thrombosis or APC-resistance was not known in the art and the specification would not enable one to practice the claimed invention. The fact that the Factor V gene may be associated with APC resistance is not sufficient description in the specification to support the claimed methods which require the identification and/or assay of mutations within the gene as no mutations are taught in the specification. In the instant case, no mutation has been identified that can be used for the prediction of increased risk, only a suggestion that such a gene exists. Furthermore, the claims explicitly recite the detection of a mutation in Factor V gene to determine the association with APC-resistance and risk of thrombosis and the specification does not teach any mutations in Factor V gene and therefore neither the specification nor the prior art enables one of skill in the art to predictably correlate any mutation in Factor V gene with the risk of thrombosis or APC-resistance.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

5. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 10am-7pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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